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Title:	Production and Purification of Radiometals for Medical Imaging
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Production and Purification of Radiometals for Medical Imaging

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Overview

- Graduate Research
- Postdoctoral Research
- Future Research

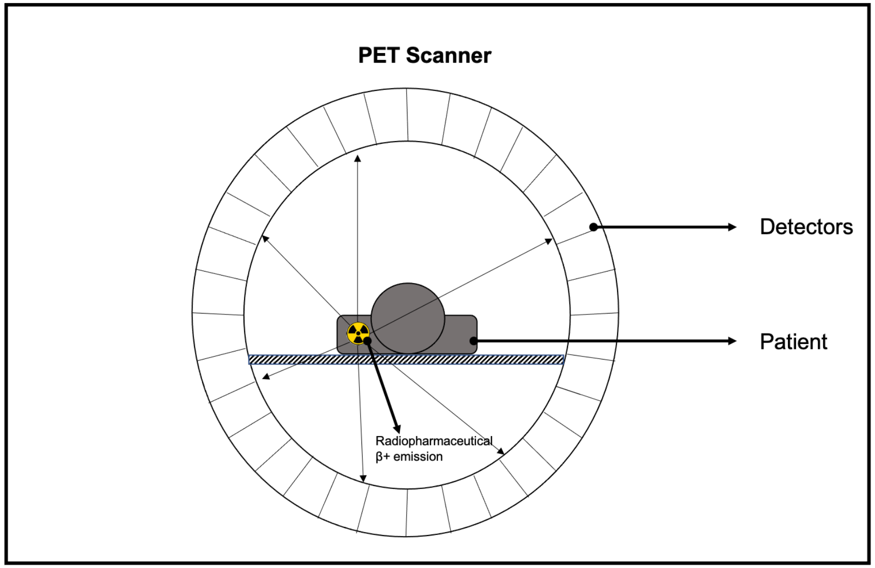
Graduate Research

- Background
- Production of ^{45}Ti
- Separation
- Development of ^{45}Ti Imaging Agents
- ^{45}Ti-labeled chelators
- In Vitro and In Vivo Evaluation of ^{45}Ti-labeled Probes

Graduate Research - Background

Positron Emission Tomography

- Imaging technique leveraging indirectly emitted gamma rays from a positron emitting radioisotope
    - Provides quantitative information about biological function and abnormalities that may be present
- Can provide insight into functional aspects of tumor biology
    - Imaging of specific receptors or molecular changes
- Can be paired with anatomical imaging (CT/MRI) for combined information about structure and function



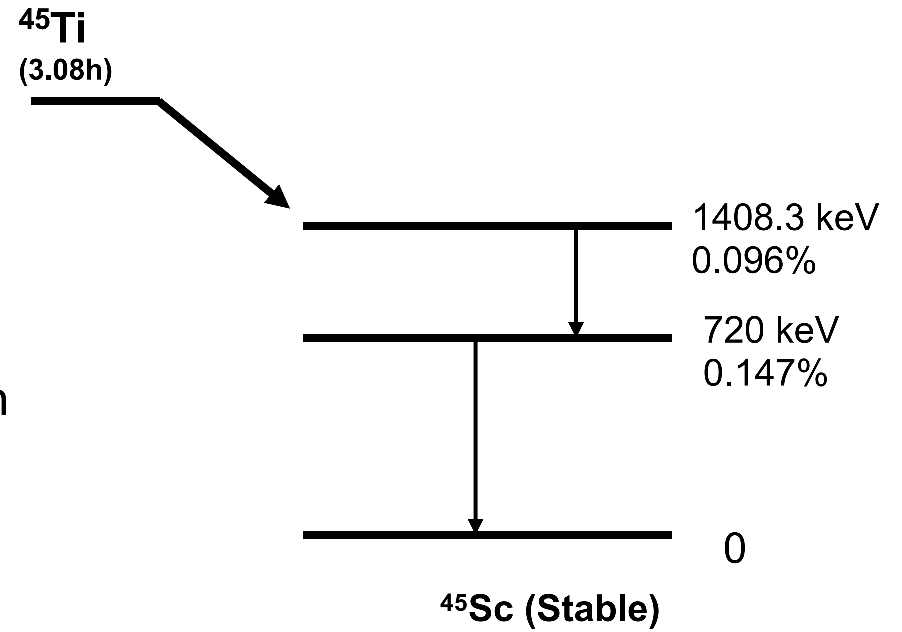
PET Radiometals

	^{68}Ga	^{89}Zr	^{45}Ti
Production	$^{68}Zn(p,n)^{68}Ga$	$^{89}Y(p,n)^{89}Zr$	$^{45}Sc(p,n)^{45}Ti$
	$^{nat}Ga(p,2n)^{68}Ge \rightarrow {}^{68}Ga$	$^{89}Y(d,2n)^{89}Zr$	
Half-life	1.2 h	78.41 h	3.08 h
Decay	90% β+, 10% EC	23% β+, 77% EC	85% β+, 15% EC
Uses	Peptide labeling	Antibody labeling	Peptide labeling, small molecules

1. Chaple I, Lapi S. Production and Use of the First-Row Transition Metal PET Radionuclides $^{43,44}Sc$, ^{52}Mn, and ^{45}Ti. J Nucl Med. 2018;59:1655-1659
2. Mojtahedi, A. et al. “The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities” (2014): 426-34

Titanium-45 Background

- Monoisotopic target
  - $^{45}Sc(p,n)^{45}Ti$
  - $T_{½}$ = 3.08 h
  - β+ = 85%
  - $β+_{avg}$ = .439 MeV
  - ^{45}Ti purification methods have been previously published (1-5)
  - PET imaging studies using nanoparticles (1), dipicolinic acid derivative ligands (2), or ^{45}Ti-Transferrin (4)



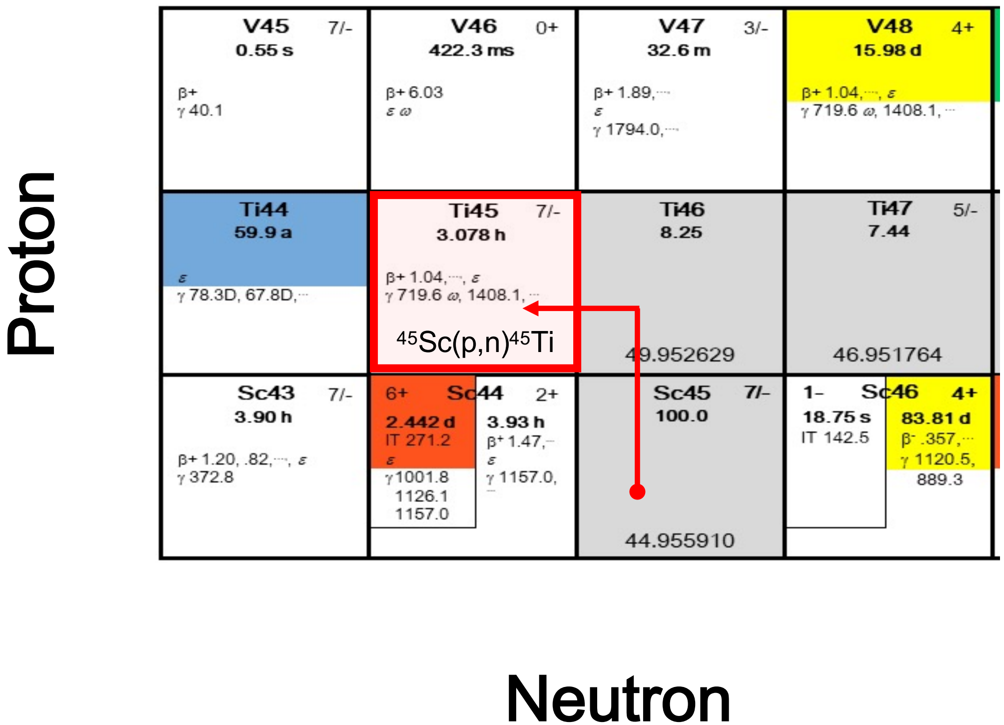
1. Chen F, Valdovinos HF, Hernandez R, Goel S, Barnhart TE, Cai W. Intrinsic radiolabeling of Titanium-45 using mesoporous silica nanoparticles. Acta Pharmacol Sin. 2017 Jun;38(6):907-913.
2. Severin GW, Nielsen CH, Jensen AI, Fonslet J, Kjær A, Zhuravlev F. Bringing Radiotracing to Titanium-Based Antineoplastics J Med Chem. 2015 Sep 24;58(18):7591-5.
3. Vavere AL, Welch MJ (2005) Preparation, Biodistribution, and Small Animal PET of 45Ti-Transferrin. Journal of Nuclear Medicine 46:683-690.

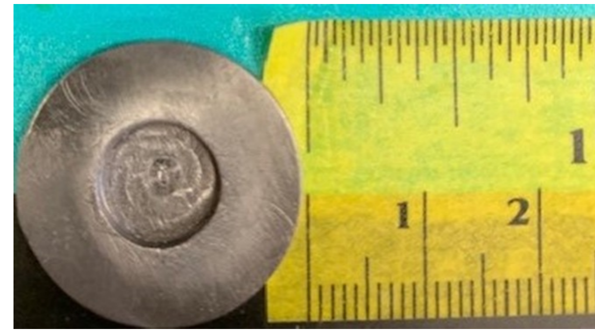
Graduate Research – Production of ^{45}Ti

UAB Cyclotron

TR-24
Advanced Cyclotron Systems, Inc.
“Blue”
15-24 MeV protons
300 μA
Solid, liquid, gas targets

Production

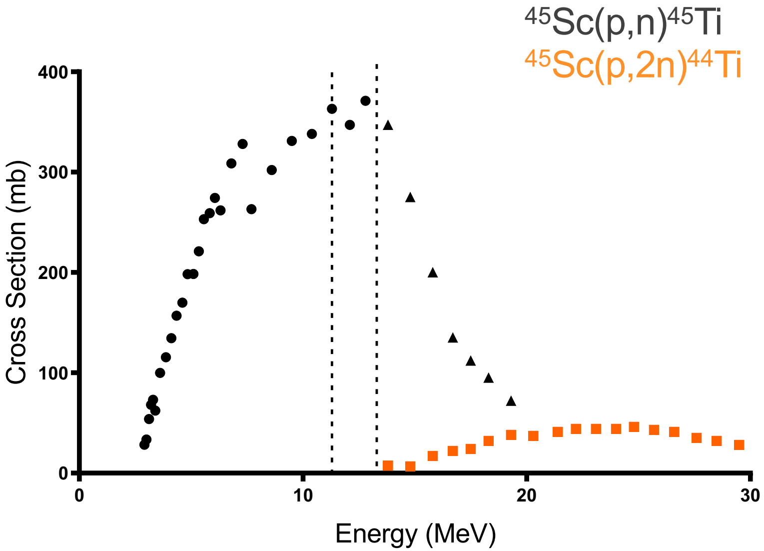


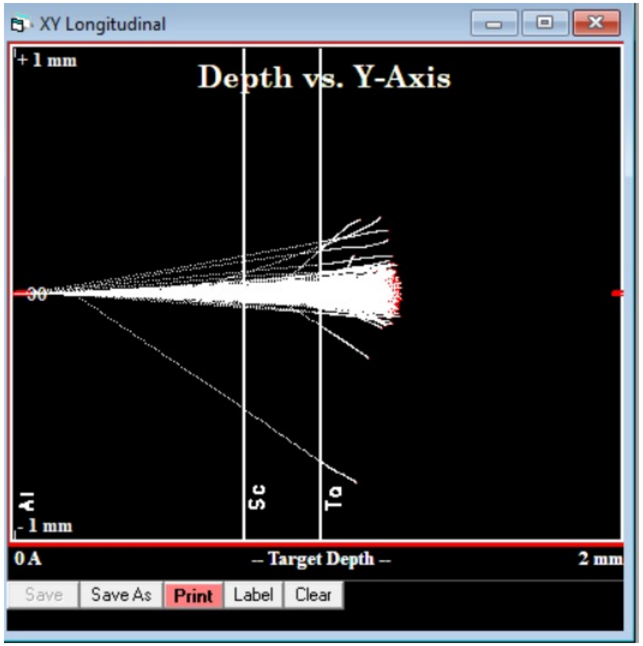


2 mm Tantalum coin

1.5 mm divot
0.75 mm Al degrader
0.1 mm retaining ring

Production



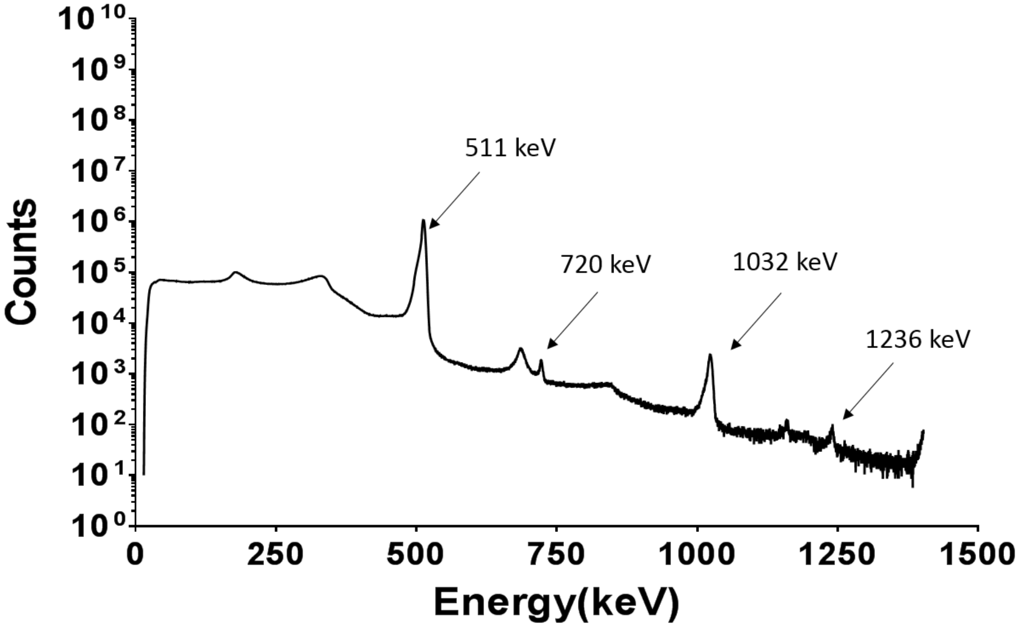


- Energy incident on Al degrader; 18 MeV
- Energy incident on Sc foil; 13.1 MeV
- Exit energy from Sc foil; 11.1 MeV

1. V. N. Levkovskii, V. F. Reutov & K. V. Botvin (1984) Helium accumulation in molybdenum irradiated by protons in the 15–30 MeV energy region, Radiation Effects, 80:3-4, 223-226
2. A.J. Howard, H.B. Jensen, M. Rios, A. W. Fowler, A.B. Zimmerman (1974) Measurement and Theoretical Analysis of Some Reaction Rates of Interest in Silicon Burning,APJ,188:,131-140

Production

- Parameters
  - 18 MeV on Al degrader
  - 13.1 MeV on Sc foil
  - 20 μA
  - 1 hour
- Produces 228 ± 7 mCi (8436 ± 259 MBq)
  - Theoretical values for a 1-hour bombardment using 20 μA current and 18 MeV protons
    - 243 mCi (9019 MBq)



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Graduate Research – Separation

Separation

Flow-through
- Dissolved foil is added to column

Wash 1
- 10 mL of 2 M HCl

Wash 2
- 10 mL MQ H_2O

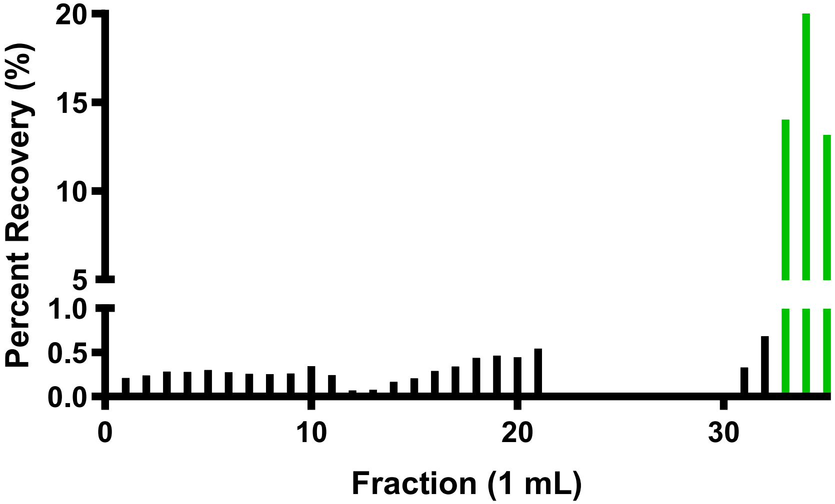
Wash 3
- 2 mL 0.1 M citric acid

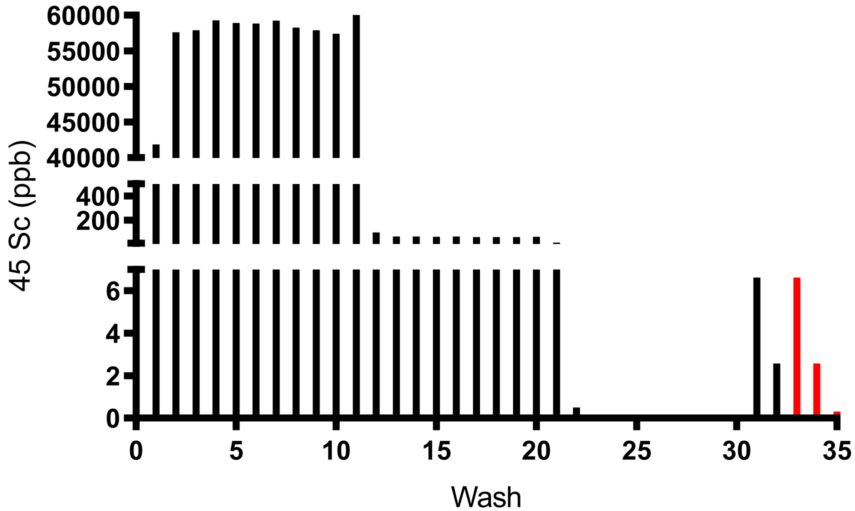
Wash 4
- 3 mL 1 M citric acid
  - Collected separately

- 129± 23 mCi total decay corrected recovery

1. Chaple, I.F., Thiele, K., Thaggard, G., Fernandez, S., Boros, E., Lapi, S.E.Optimized Methods for Production and Purification of Titanium-45. Applied Radiation and Isotopes 166:109398.

Separation



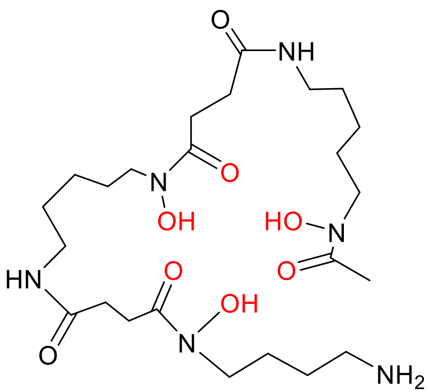


Elemental analysis using ICP-MS showed that in the final fractions (33-35; shown in red) where ^{45}Ti was collected, there was very little breakthrough of the scandium target material (0.027 µg).

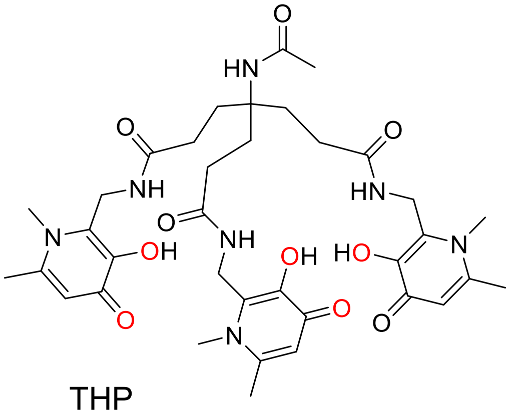
1. Chaple, I.F., Thiele, K., Thaggard, G., Fernandez, S., Boros, E., Lapi, S.E.Optimized Methods for Production and Purification of Titanium-45. Applied Radiation and Isotopes 166:109398.

Graduate Research – ^{45}Ti-labeled chelators

Chelators



DFO

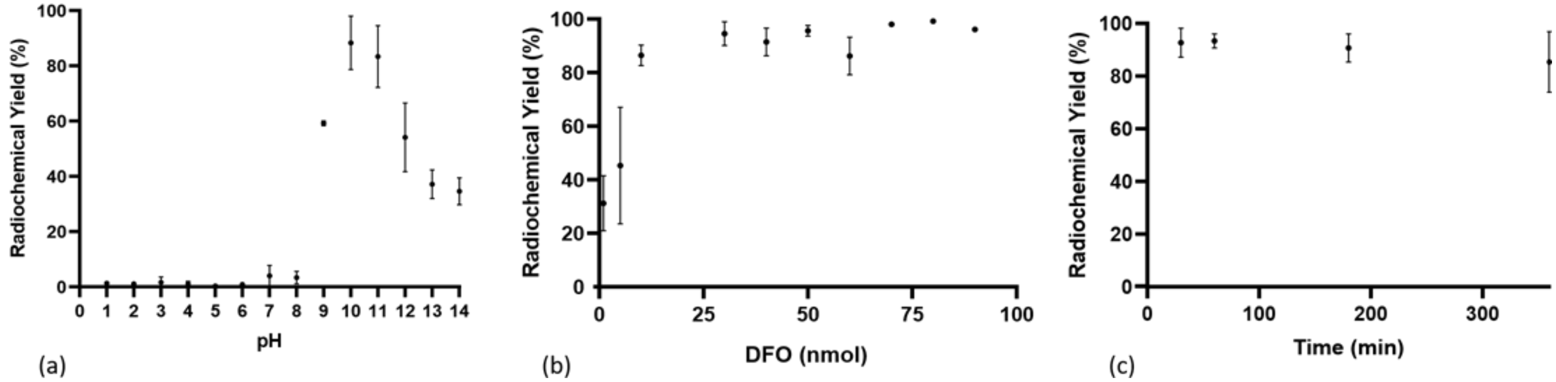


THP

- Deferroxamine (DFO) widely used with ^{89}Zr (1)
- Tris(hydroxypiridinone) (THP) used with ^{68}Ga (2)

1. Zeglis, B. M., & Lewis, J. S. (2015). The bioconjugation and radiosynthesis of 89Zr-DFO-labeled antibodies. *Journal of visualized experiments : JoVE*, (96), 52521.
2. Derlin T, Schmuck S, Juhl C, Teichert S, Zörgiebel J, Wester HJ, Schneefeld SM, Walte ACA, Thackeray JT, Ross TL, Bengel FM. Imaging Characteristics and First Experience of [^{68}Ga]THP-PSMA. Mol Imaging Biol. 2018 Aug;20(4):650-658.

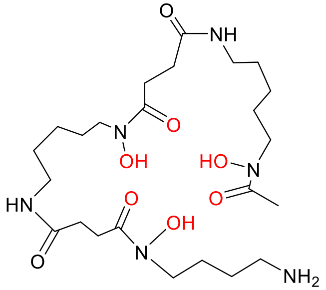
^{45}Ti-DFO



A pH optimization of ^{45}Ti-DFO formation (a).

Radiochemical yields of ^{45}Ti complexation with varying nmol amounts of DFO (b).

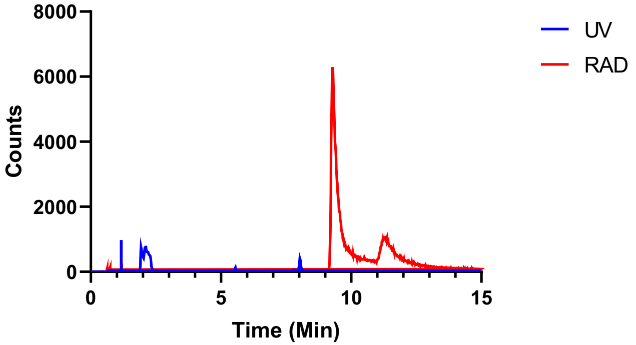
Mouse serum stability studies were completed up to six hours post incubation (c).



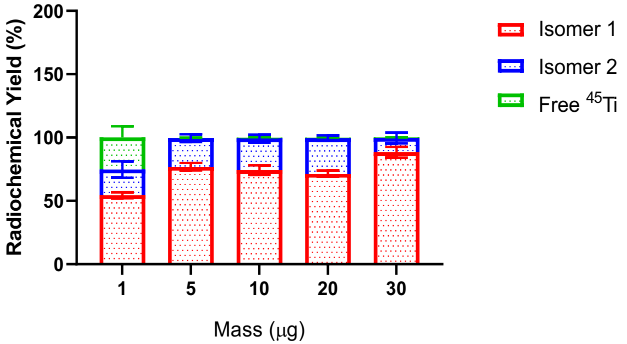
DFO

1. Chaple I, Lapi S. Production and Use of the First-Row Transition Metal PET Radionuclides $^{43,44}Sc$, ^{52}Mn, and ^{45}Ti. J Nucl Med. 2018;59:1655-1659

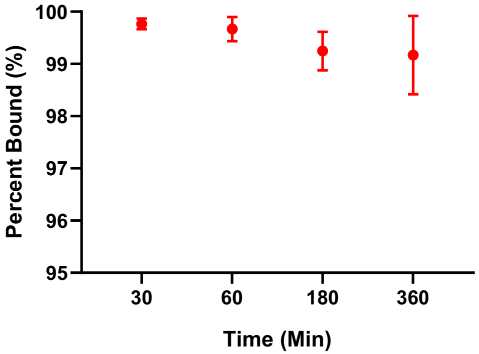
^{45}Ti-THP



(a)



(b)

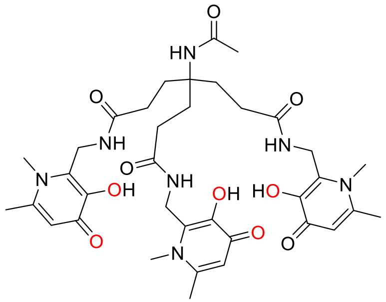


(c)

^{45}Ti-THP formation HPLC (a).

Radiochemical yields of ^{45}Ti complexation with varying amounts of THP (b).

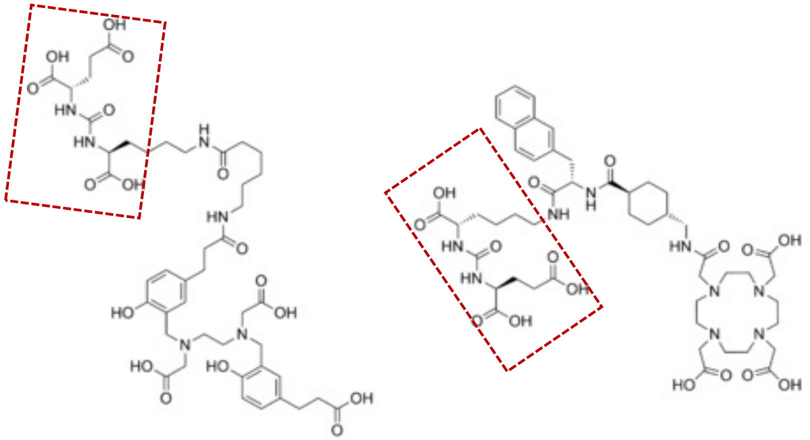
Mouse serum stability studies were completed up to six hours post incubation (c).



Graduate Research – In Vitro and Vivo Evaluation of ^{45}Ti-labeled Probes

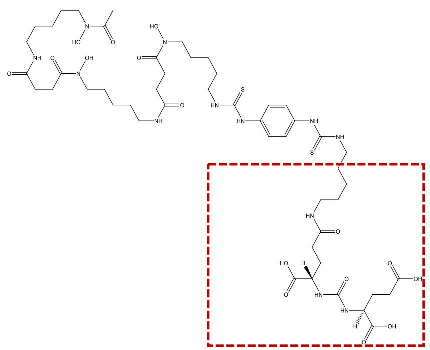
Prostate Specific Membrane Antigen

- Prostate cancer is the second leading cause of death due to cancer among men in the United States
- PSMA was discovered and cloned in 1993 (1)
  - 100 kDa
  - Type II transmembrane glycosylated protein
  - Also known as glutamate carboxypeptidase II (2)
  - Expressed in low levels on kidneys, salivary glands, and prostate tissue
  - Overexpressed on prostate cancer cells
- ^{68}Ga-PSMA-11
  - Used for diagnostic PET imaging
- ^{177}Lu-PSMA-617
  - Used for targeted therapy



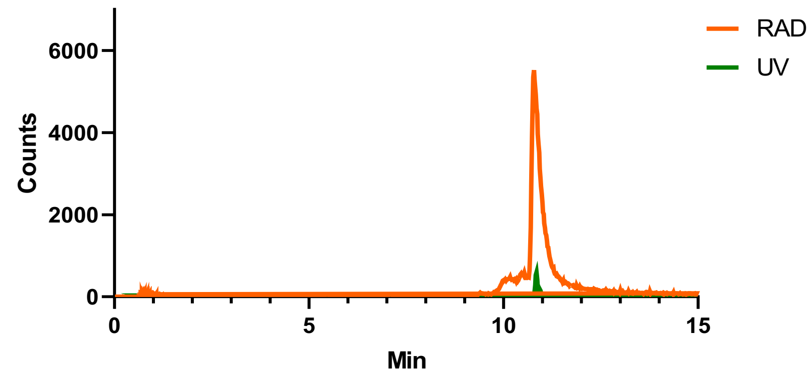
1. Israeli, R.S., Powell, C.T., Fair, W.R., Heston, W.D.W. 7003413080;54903870200;7101676287;7004282254; Molecular Cloning of a Complementary DNA Encoding a Prostate-specific Membrane Antigen (1993) Cancer Research, 53 (2), pp. 227-230
2. Lv Q, Yang J, Zhang R, et al. Prostate-Specific Membrane Antigen Targeted Therapy of Prostate Cancer Using a DUPA-Paclitaxel Conjugate. *Mol Pharm. 2018;15:1842-1852.*

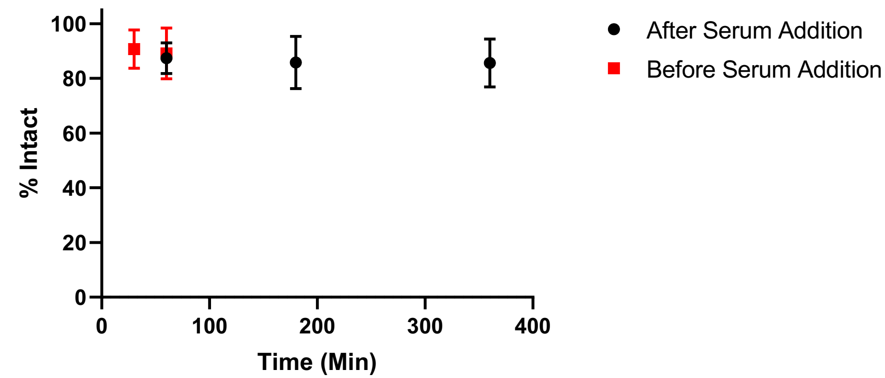
^{45}Ti-DFO-DUPA Stability



DFO

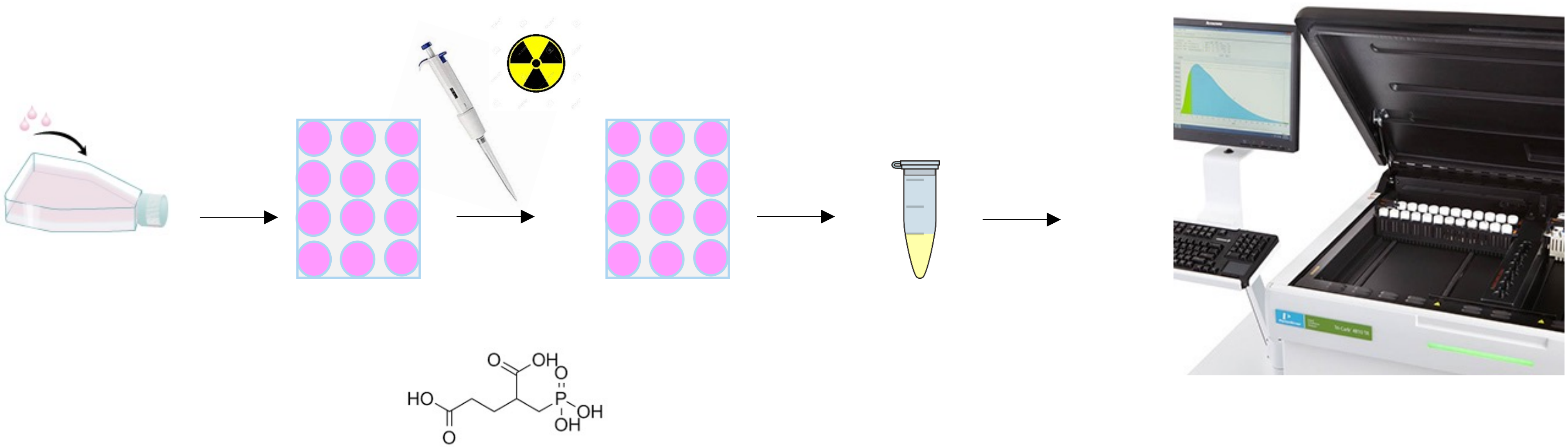
DUPA



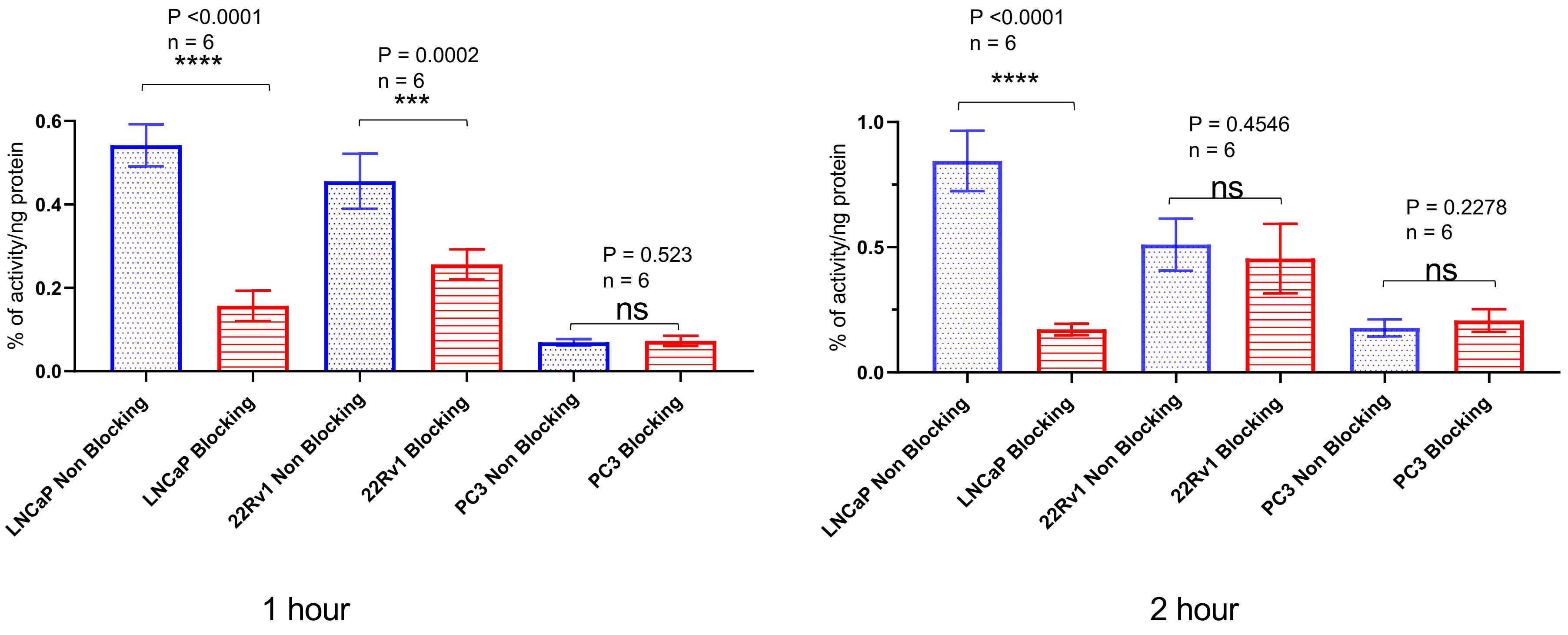


- 70 nmol DFO-DUPA
  - Labeled with 500 µCi ^{45}Ti
  - pH 11
  - 50°C and 800 RPM for 45 min
- After 1 hour, 900 µL whole mouse serum was added and kept at 50°C, 800 RPM.

Study Preparation



^{45}Ti-DFO-DUPA Cell Uptake



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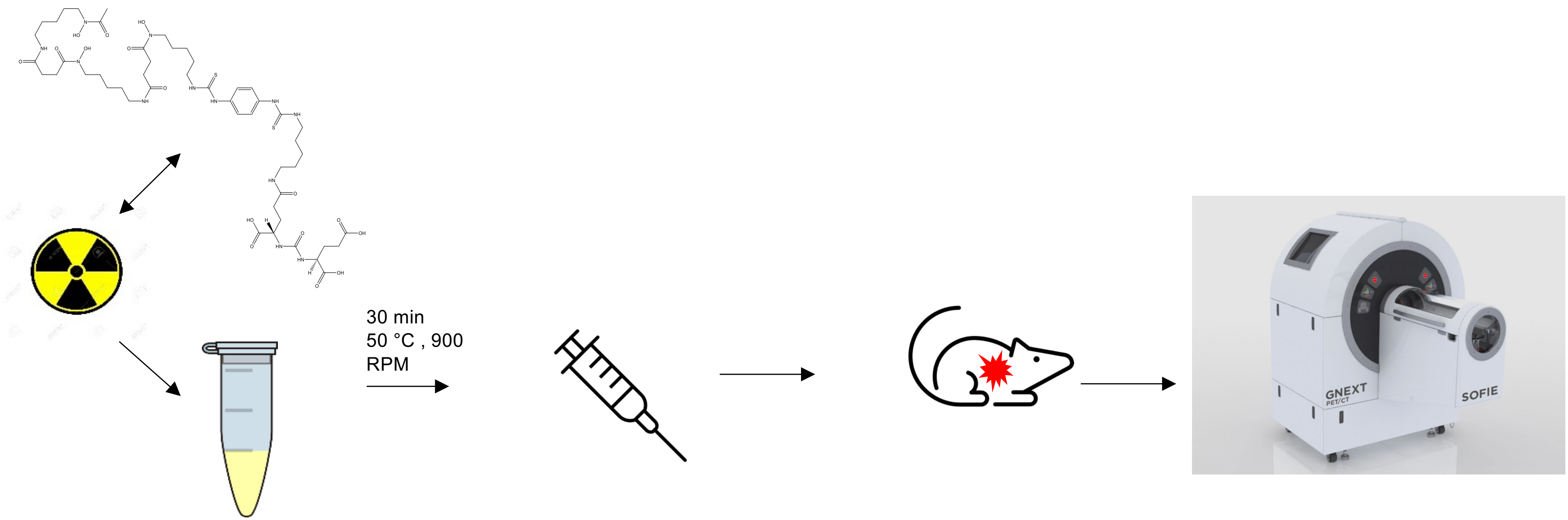
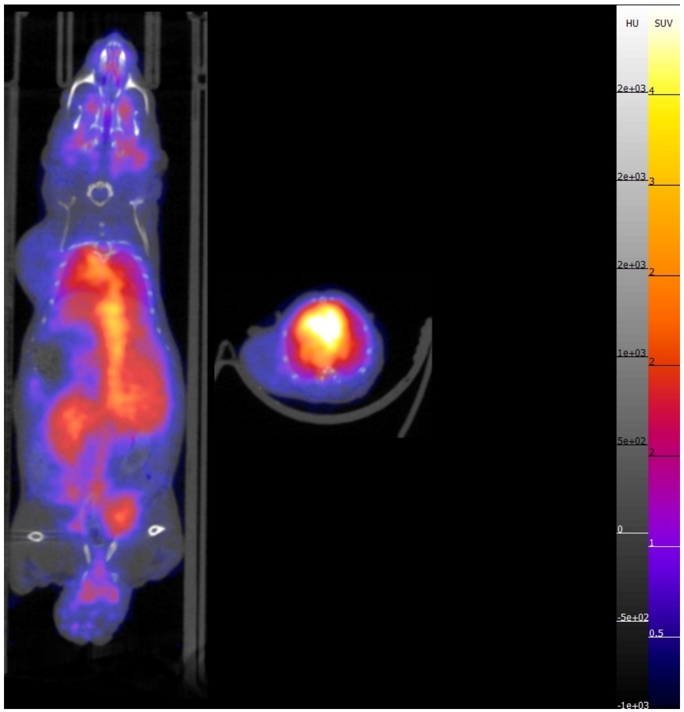
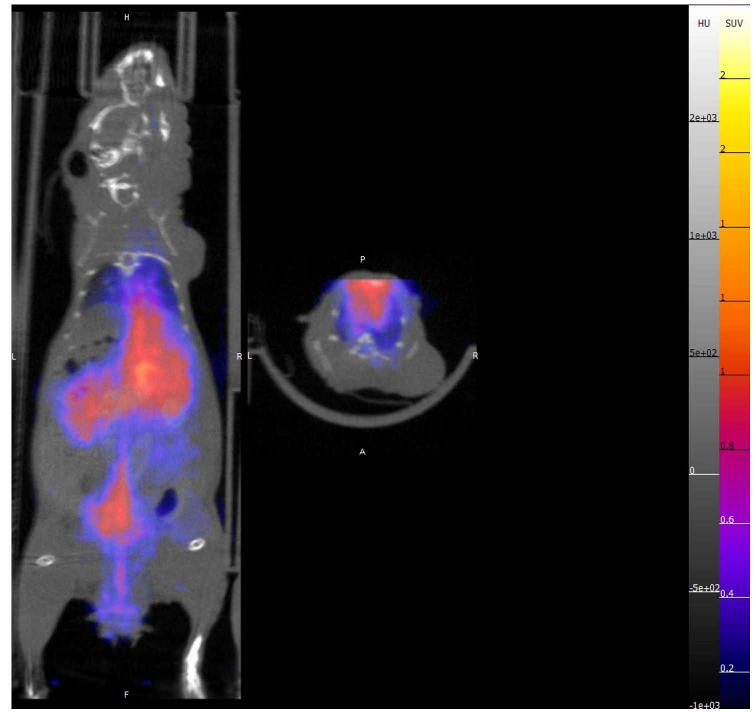
^{45}Ti-DFO-DUPA Animal Study



PET/CT Images

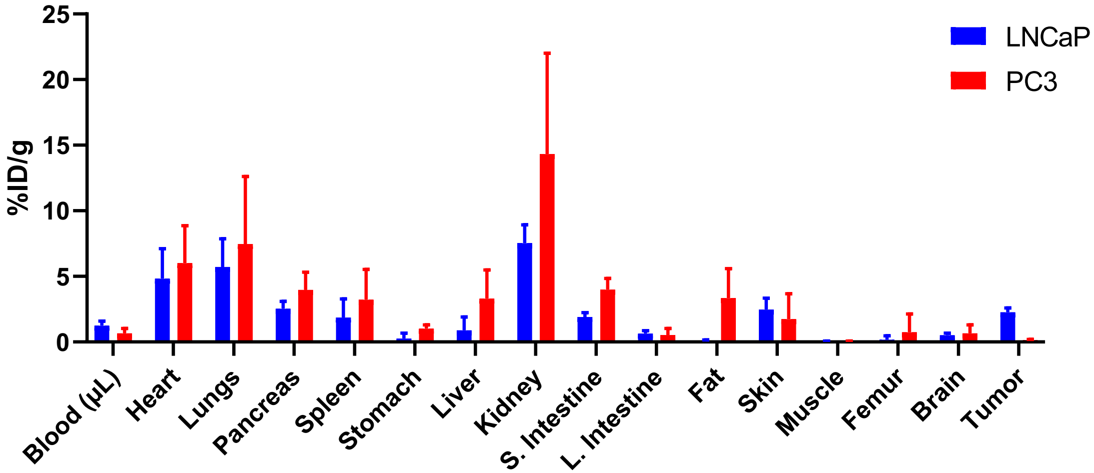


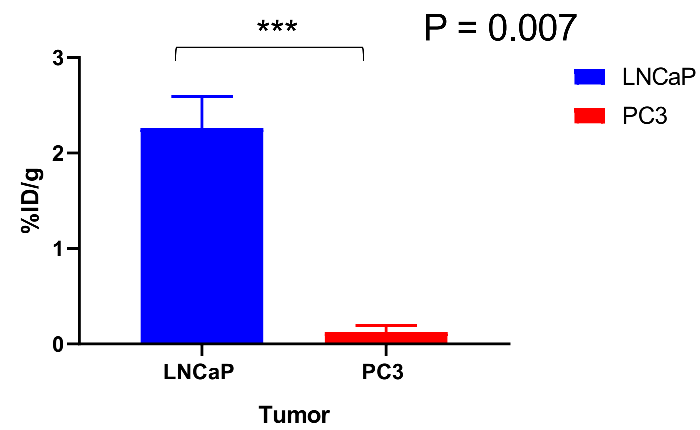
LNCaP, 1 hour



PC3, 1 hour

PSMA+ vs. PSMA- Tumor Uptake





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Postdoctoral Research

- Background
- Resin Synthesis
- Preliminary Results

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Postdoctoral Research – Background

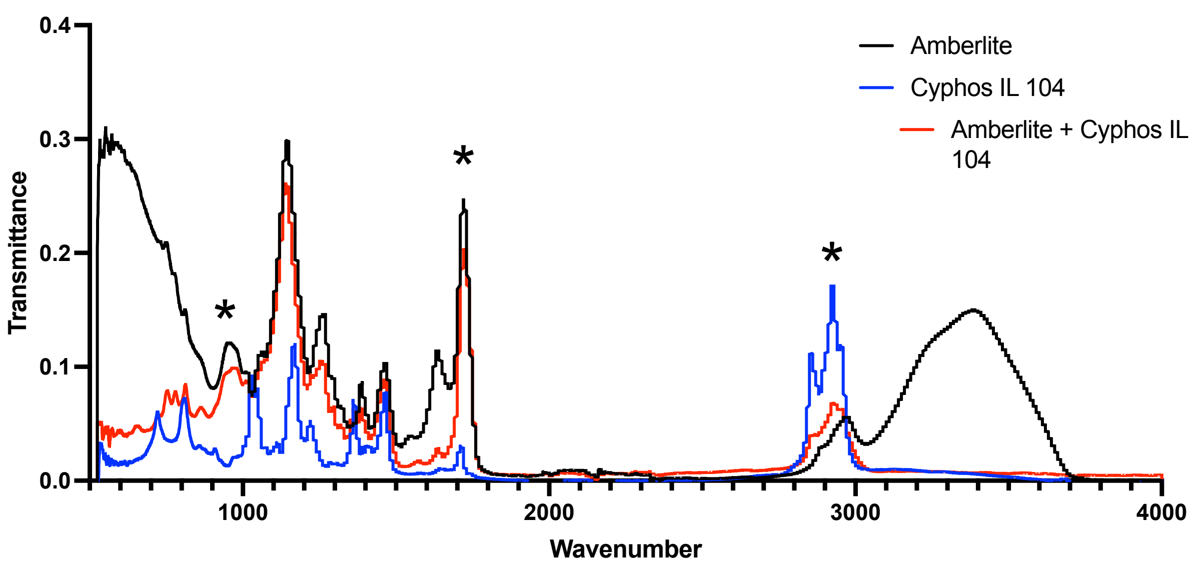
Background

- Lanthanides (4f elements) find use in various everyday technologies, while actinides (5f elements) play an important role in nuclear energy applications.
- Lanthanides are considered critical materials, and the development of lanthanide chemical separation methods is paramount for recovery, recycling and purification purposes.
- Radiolanthanides also find use as clinical diagnostic (^{152}Tb, ^{140}Nd) and therapeutic (^{177}Lu, ^{161}Tb) agents.
- Lanthanide separation from each other is difficult due to the nearly identical chemical properties.
- In order to meet the goal of efficient lanthanide separation, IL extractants will be evaluated for liquid-liquid extraction efficiency.

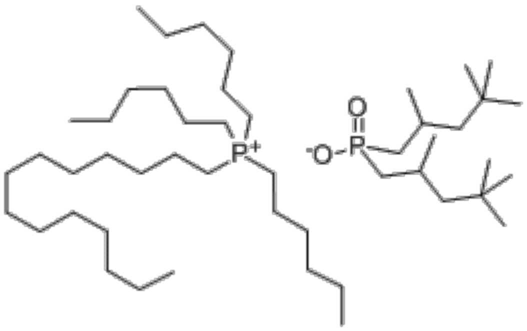
Postdoctoral Research – Resin Synthesis

Resin Synthesis

Cyphosil 104 Impregnated Amberlite



- Peak at 983 cm^{-1} shifted to 947 cm^{-1} when functionalized due to stretching vibration of the bond Cr-O
- Peaks at 2930cm^{-1}, 2859 cm^{-1}, and 2957 cm^{-1} are stretching vibrations of CH_3 and CH_2 in Cyphos IL 104
- Peak at 1735 cm^{-1} is the vibration of C=O in resin



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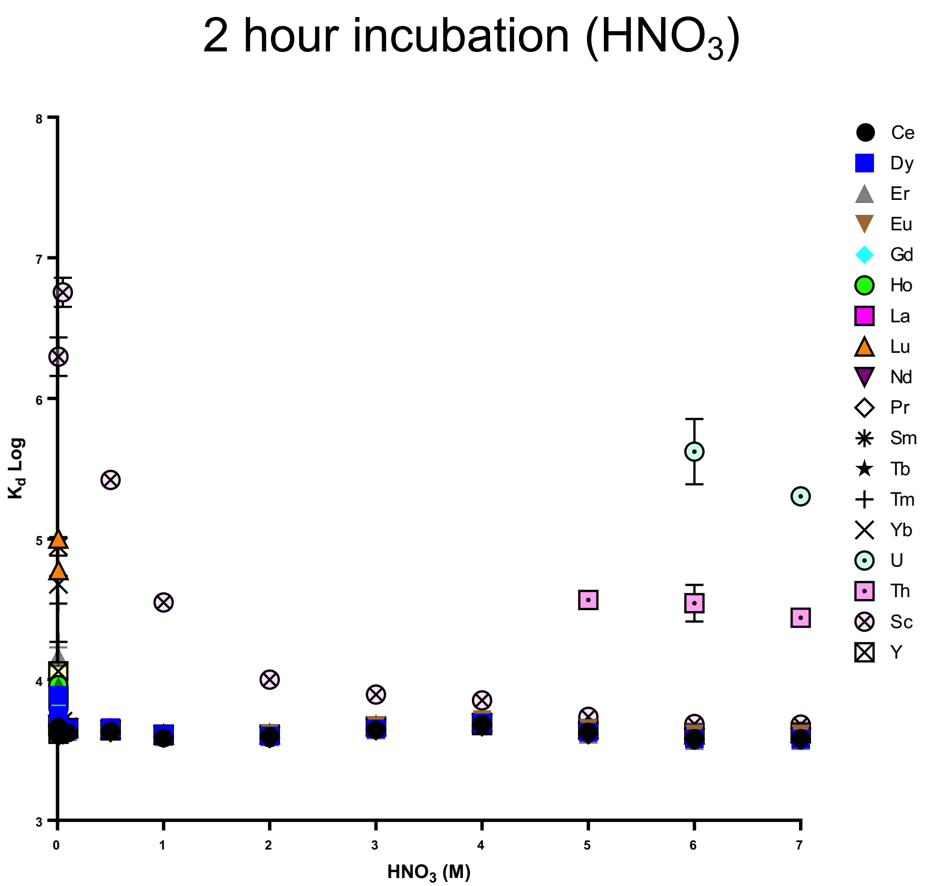
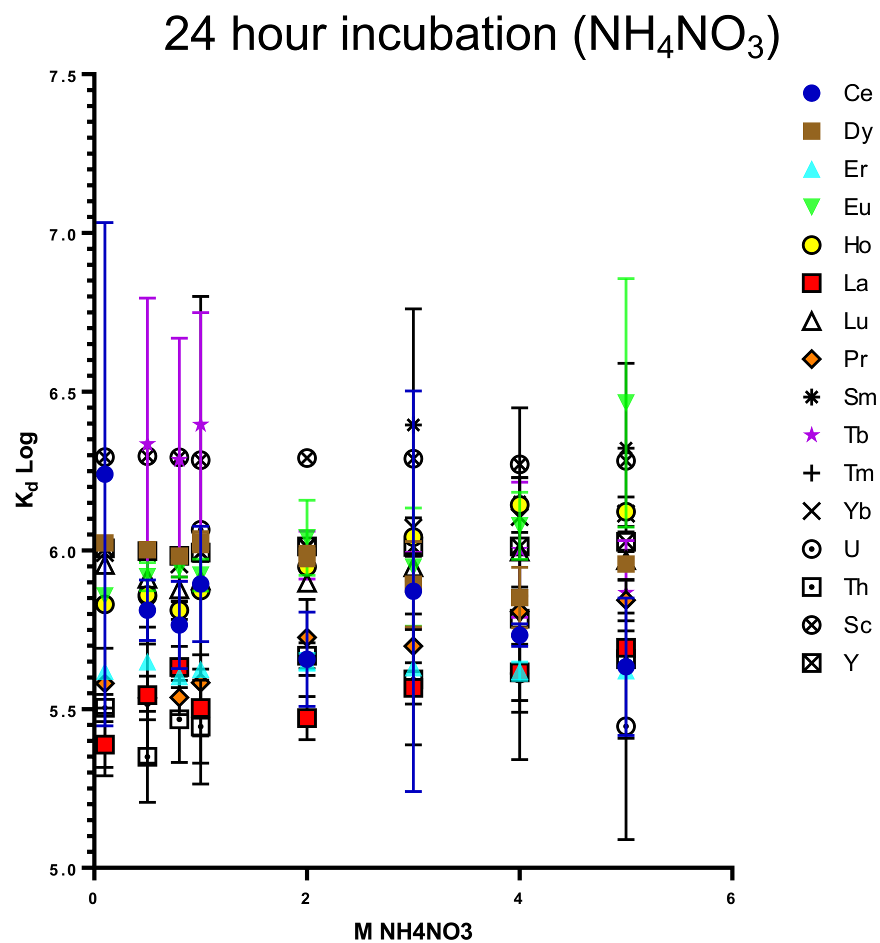
Postdoctoral Research – Preliminary Results

Preliminary Results





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Future Research

- Future Directions

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Future Research – Future Directions

Future Directions

- Production of medically relevant radioisotopes
  - Lanthanides; ^{165}Dy, ^{161}Tb, ^{177}Lu.
  - Actinides; ^{225}Ac, ^{227}Th.
  - Other Radiometals; $^{44/47}Sc$, ^{64}Cu, ^{55}Co.
- Development of novel separation methods
  - Ion chromatographic methods
  - Ionic liquids
- Radiochemistry
  - Research and development of radiopharmaceuticals
  - Bifunctional chelators and receptor targeted ligands

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- Veronika Mocko, Ph.D.

- University of Alabama at Birmingham
- Suzanne Lapi, Ph.D.

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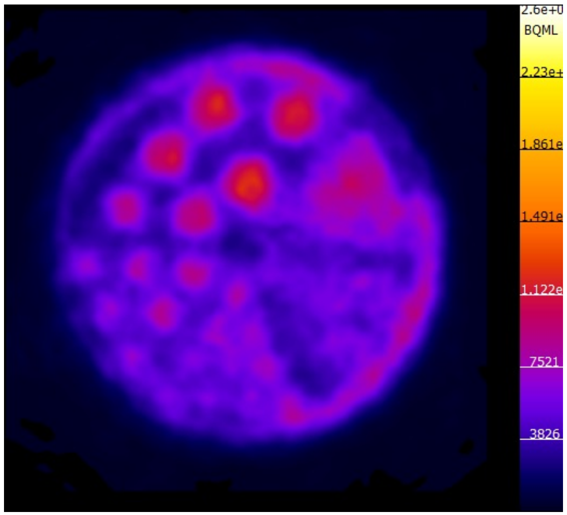
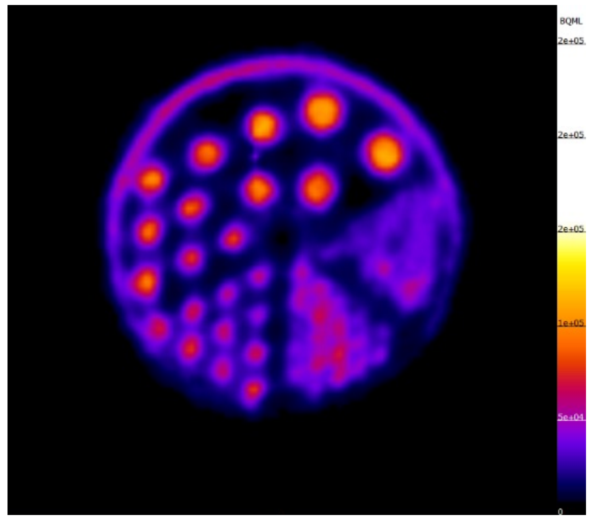
- ERF SNMMI Predoctoral Molecular Imaging Grant
    - 338650.01.01.2020984.10

Thank you!

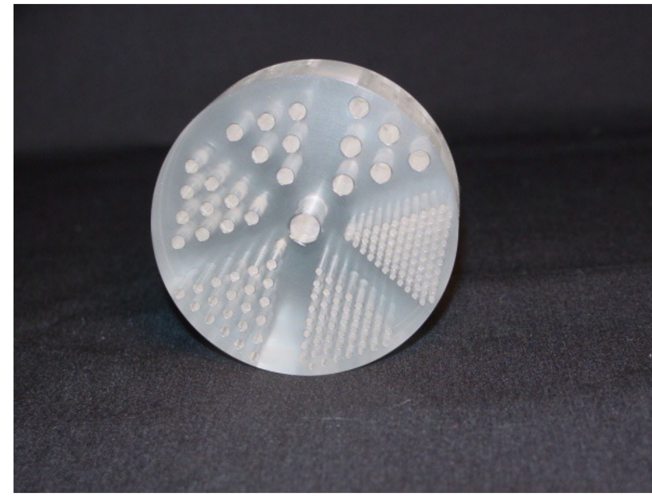
Derenzo Phantom



^{68}Ga



^{45}Ti



1.2, 1.6, 2.4, 3.2, 4.0 and 4.8 mm

- 3.7 MBq (100 µCi) of ^{45}Ti was diluted to 15 mL of 18 MQ H2O and added to a miniature Derenzo phantom (Data Spectrum Corporation).
- 60-min scan on the UAB small animal PET scanner (GNEXT PET/ CT, Sofie Biosciences, CA).

1. Chaple, I.F., Thiele, K., Thaggard, G., Fernandez, S., Boros, E., Lapi, S.E.Optimized Methods for Production and Purification of Titanium-45. Applied Radiation and Isotopes 166:109398.

PSMA Blocking Study